REMARKS

Status of the Claims

Claims 1-11 and 14 are currently pending in the application. Claims 1-6, 9, 10, 12 and 13 stand rejected. The Examiner objects to claims 2, 9 and 10. Claims 7, 8, 11 and 14 are withdrawn as being drawn to a non-elected invention. Claims 1-6 and 8-10 have been amended as set forth herein. Claims 12 and 13 have been cancelled herein. All amendments and cancellations are made without prejudice or disclaimer. No new matter has been added by way of the present amendments. Specifically, the amendment to claim 1 is supported by the specification at, for instance, pages 26-27. Amendments to other claims are non-limiting amendments and are to conform the claim language more closely to US practice. Reconsideration is respectfully requested.

Objections to the Claims

The Examiner objects to claims 2, 9 and 10. (*See*, Office Action of May 19, 2006, at page 2, hereinafter, "Office Action"). The Examiner states that claim 2 appears to embrace cultured conditions which give rise to "embryoid bodies" but the claim suggests culture conditions for the creation of "embryonic bodies." Thus, the Examiner requests correction. Claim 2 has been amended to correct the phrase as the Examiner suggests. This is a non-limiting amendment.

The Examiner also states that claims 9 and 10 begin with grammatically incorrect preambles. Claims 9 and 10 have been amended herein without prejudice or disclaimer to correct the grammar in the preamble of these claims. These are non-limiting amendments.

Reconsideration and withdrawal of the objections to claims 2, 9 and 10, in light of the amendments made thereto, are respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-6, 9, 10, 12 and 13 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. (*See*, Office Action, at page 3). Claims 12 and 13 have been cancelled herein without prejudice or disclaimer, thus obviating the rejection as to claims 12 and 13. Applicants traverse the rejection as to the remaining claims as set forth herein.

The Examiner states that the specification discloses a method for inducing differentiation of pluripotent embryonic stem cells (ESC) into functioning cells and the transplantation of said cells into a mammalian patient. (*Id.*). The Examiner further states that while the specification contemplates production of pancreatic islet like cell clusters, the specification does not provide any disclosure or guidance (working examples) for the production of mammalian functional pancreatic islet like cell clusters and treating any mammalian patient with diabetes and related disorders with the cell clusters. (*Id.* at pages 3-4).

However, claim 1, as amended, recites,

"A method for inducing differentiation of mammalian embryonic stem cells into insulin producing cells, which comprises the steps of: (A) culturing mammalian embryonic stem cells together with feeder cells with a medium comprising leukemia inhibitory factor; (B) culturing the cells obtained from step (A) in absence of feeder cells with a medium comprising leukemia Inhibitory factor and basic FGF in a suspension culture condition to give embryoid bodies; (C) culturing the obtained embryonic bodies with a selection-expanding medium; and (D) culturing the cells obtained from step (C) with a differentiation medium to give insulin producing cells." More specifically, the Examiner's attention is directed to part (D) of claim 1 wherein the claim recites, in part, "to give insulin producing cells" instead of the phrase "functioning cells."

Although the definition of "functioning cells," at least within the context of the presently claimed invention and the present disclosure, is provided at pages 25-27 of the as-filed specification, and is defined in terms of the expression of several genes critical for pancreatic islet-like cell functioning, to expedite prosecution, Applicants have amended claim 1 to more clearly define the subject matter encompassed by the claim. That is, claim 1 has been amended to recite in step (D) "insulin-producing cells" rather than "functioning cells." Thus, at least as amended, claim 1 does not lack enablement since it is clearly supported by the as-filed specification, at, for instance, pages 26-27. The disclosure proves that using the presently claimed method, insulin-producing cells may be obtained.

To further support this point, attached hereto please find a copy of Segev et al., *Stem Cells*, 22:265-274, 2004, disclosing that one of ordinary skill in the art knows that the differentiation methods disclosed in the presently claimed invention, as demonstrated with mES cells, also work very well for human ES cells. (Copy of Segev et al. attached hereto as Exhibit A, for the Examiner's convenience). Thus, it is common in the art to use mouse ES cells to prove that methods for differentiating human ES cells work. Mouse ES cells are more often used due to the increased expenses associated with human ES cells.

Reconsideration and withdrawal of the enablement rejection of claims 1-6, 9 and 10 are respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 4 stands rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. (*See*, Office Action, at page 11). Applicants traverse the rejection as set forth herein.

The Examiner states that claim 4 is indefinite for reciting the phrase "the obtained cell cluster" in line 1. (*Id.*).

The Examiner is mistaken. Claim 4 does not recite this phrase. Claim 4 recites, "The method of claim 1, wherein the medium used in step (C) comprises nicotinamide, insulin and fibronectine in a serum-free cell culture medium." Thus, the rejection is moot.

However, Applicants see that claim 1, part (D) recites this phrase. The phrase, "the obtained cell cluster" in part (D) of claim 1 has been amended to recite, "culturing the cells obtained from step (C) with a differentiation medium to give insulin producing cells." Thus, it is believed the supposed rejection has been overcome by this amendment.

Reconsideration and withdrawal of the indefiniteness rejection of claim 4 is respectfully requested.

Rejections Under 35 U.S.C. § 102(a)

Claims 9 and 10 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Lumelsky et al., *Science*, 292, 19 May 2001, 1388-1394 (hereinafter referred to as "Lumelsky et al."). (*See*, Office Action, at pages 11-12). Applicants traverse the rejection as set forth herein.

The Examiner states that Lumelsky et al. disclose ESC that differentiate and secrete insulin. The Examiner states that Lumelsky et al. further disclose induction of ESC to functioning insulin secreting cells through steps similar to those recited in claim 1. (*Id.* at page 12).

The method disclosed by Lumelsky et al. differs from the presently claimed method in several ways, thus Lumelsky et al. cannot anticipate the presently claimed method.

First, in Lumelsky et al., no LIF is used in the ES cell media for EB formation. In contrast, the present method provides for the use of ES cell media containing LIF and bFGF.

Second, Lumelsky et al. divide the selection and expansion stage into two stages (stages 3 and 4). However, in contrast, the presently claimed invention performs this in one step, step 3. The preferred media comprises nicotinamide, fibronectin and N2 supplements.

Third, the presently claimed method calls for N2 and nicotinamide from the selection through to the differentiation stage. Also, laminin is added in the differentiation media for differentiating insulin-producing cells.

Fourth, ultrastructure and function of the differentiated insulin-producing cells of the presently claimed methods are different compared to those of Lumelsky et al. That is, according to the instantly claimed invention, insulin-producing cells differentiated from mES cells had an ultrastructure similar to beta cells. As disclosed in the Examples of the presently claimed invention, these cells were grafted in rats in which STZ was used to induce diabetes. It is shown in the present specification that in these rats, blood glucose levels were restored. The differences in ultra structure and function between the presently claimed invention and that of Lumelsky et al. are highlighted further by Rajagopal et al., *Science*, 299:363, 2003. (Copy attached hereto as Exhibit B, for the Examiner's convenience).

Thus, at least for this reason, the disclosure of Lumelsky et al. cannot anticipate the presently claimed invention as recited in claims 9 and 10 because the disclosure of Lumelsky et al. does not disclose each and every limitation of the presently claimed invention. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or

inherently described, in a single prior art reference." (*See, Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987)).

Reconsideration and withdrawal of the anticipation rejection of claims 9 and 10 are respectfully requested.

Rejections Under 35 U.S.C. § 102(e)

Claims 1-6 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Thomson et al., U.S. Patent No. 6,602,711 (hereinafter referred to as "Thomson et al."). (*See*, Office Action, at page 12). Applicants traverse the rejection as set forth herein.

The Examiner states that Thomson et al. disclose a method of making embryoid bodies from primate embryonic stem cells by culturing the primate embryonic stem cells together with feeder cells in media containing leukemia inhibitory factor ("LIF"), removing these colonies and leaving the ES cells in suspension during further embryoid body formation. (*Id.* at pages 12-13).

In fact, there is no mention anywhere in the disclosure of Thomson et al. of the use of LIF to culture mammalian ESC. Referring specifically to the bottom of column 3 to column 4, Thomson et al. disclose a detailed description of the preferred embodiment, which is the formation of embryoid bodies, not the formation of insulin-producing cells therefrom. At the bottom of column 4 and continuing on to the top of column 5, Thomson et al. disclose how these embryoid bodies are analyzed using the Force-1 antibody to find the expression of neuron-specific proteins. At the bottom of column 5 Thomson et al. disclose possible routes to differentiation of the embryoid bodies into other tissues such as cardiac lineages and neural lineages. There is no mention anywhere in Thomson et al. of culturing mES cells with feeder cells in a medium comprising LIF (step A of presently pending claim 1). Actually, there is no

disclosure anywhere in Thomson et al. of any of the four steps of presently pending claim 1. Neither LIF nor FGF are mentioned in Thomson et al., nor even insulin or cells that may produce insulin, or how such cell activity might be measured or obtained.

Thus, the disclosure of Thomson et al., being utterly devoid of any suggestion or disclosure of the presently claimed method, fails to disclose each and every limitation of the presently claimed invention and cannot be the basis of any anticipation rejection of the presently claimed invention, as recited in claim 1.

Dependent claims 2-6 are not anticipated as, *inter alia*, depending from a non-anticipated base claim, claim 1.

Reconsideration and withdrawal of the anticipation rejection of claim(s) . . . are respectfully requested.

CONCLUSION

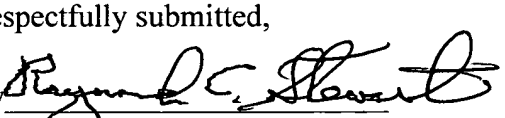
Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of $225.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Thomas J. Siepmann, Ph.D. (Reg. No. 57,374) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: October 19, 2006

Respectfully submitted,

By 

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Attachments: Exhibit A – Hanna SEGEV et al., *Stem Cells*, Vol. 22 (2004), pp.265-274.

Exhibit B – Jayaraj RAJAGOPAL et al., *Science*, Vol. 299, (Jan. 17, 2003), p.263.

TJB